A Phase 2, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Palovarotene in Subjects with Multiple Osteochondromas

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Primary Objective• To evaluate the efficacy of two dosage regimens of palovarotene compared with placebo in preventing new osteochondromas (OCs) in subjects with multiple osteochondromas (MO) due to exostosin 1 (Ext1) or exostosin 2 (Ext2) mutations...

Ethical review	Approved WMO
Status	Completed
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Interventional

Summary

ID

NL-OMON48469

Source
ToetsingOnline

Brief title
MO-Ped

Condition

- Musculoskeletal and connective tissue disorders congenital

Synonym
Multiple Osteochondromas or Multiple Hereditary Exostoses

Research involving
Human

Sponsors and support

Primary sponsor: Clementia Pharmaceuticals Inc

Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Multiple Osteochondromas, Paediatric, Palovarotene, Phase 2

Outcome measures

Primary outcome

Preventing new osteochondromas (OCs) in subjects with multiple osteochondromas (MO) due to exostosin 1 (Ext1) or exostosin 2 (Ext2) mutations when comparing palovarotene with placebo.

Secondary outcome

Secondary objectives will be to compare the following effects of palovarotene with placebo:

• The volume of OCs as assessed by magnetic resonance imaging (MRI).

• The proportion of subjects with no new OCs.

• The rate of new or worsening skeletal deformities.

• The rate of MO-related surgeries.

Additional secondary objectives:

• Overall palovarotene safety.

• The pharmacokinetics of palovarotene at steady state.

• The palatability of drug product when sprinkled onto specific foods.

Exploratory Objectives

Exploratory objectives will be to compare the following effects of palovarotene with placebo:

• The changes in volume of OC cartilage caps as assessed by MRI.

• The rate of new or worsening functional limitations.

• Pain and pain interference due to OCs.

• Quality of life.

Study description

Background summary

Multiple osteochondromas (MO), or multiple hereditary exostoses (MHE), is an autosomal-dominant skeletal disorder primarily caused by loss-of-function mutations in exostosin 1 (Ext1) or exostosin 2 (Ext2) genes. Although rare, with prevalence estimates in the United States (US) and Europe at 1 per 50,000 population, MO is among the most common inherited skeletal disorders.
The key clinical features of MO are benign cartilage-capped bone tumors emerging from the growth plates of long bones, ribs, vertebrae, and pelvis, known as osteochondromas (OCs).
Osteochondromas begin to develop and continue to grow during the first and second decades of life, and cease development and growth when growth plates close at puberty. Thus, MO is a disease that manifests exclusively in children, with a mean diagnosis/onset of about 4 years of age.
Currently there is no medicinal treatment to prevent the development of OCs and the clinical sequelae of skeletal deformities, functional limitations, and pain. Surgical excisions are performed when OCs cause pain, restrict function, or lead to cosmetic complaints, but carry a risk of irreversible damage to growth plates. Thus, there is a significant unmet medical need for a medicinal therapy to prevent the formation and growth of OCs.
It is hypothesized that palovarotene compared to placebo will prevent the formation of new OCs in subjects with MO.
The primary objective of Study PVO-2A-201 is to compare the efficacy of two dosage regimens of palovarotene with placebo in preventing the formation of new OCs in subjects with MO due to Ext1 or Ext2 mutations.
Secondary study objectives are to compare the effect palovarotene treatment with placebo on the volume of OCs and on the proportion of subjects with no new OCs as assessed by whole body MRI; and on the annualized rates of new or worsening skeletal deformities and MO-related surgeries. The overall safety of palovarotene and treatment effects on linear growth and the growth plate will also be evaluated. The pharmacokinetics of palovarotene at steady-state will also be evaluated as a secondary objective.

Study objective

Primary Objective

• To evaluate the efficacy of two dosage regimens of palovarotene compared with placebo in preventing new osteochondromas (OCs) in subjects with multiple osteochondromas (MO) due to exostosin 1 (Ext1) or exostosin 2 (Ext2) mutations.
Secondary Objectives
Secondary objectives will be to compare the following effects of palovarotene with placebo:
• The volume of OCs as assessed by magnetic resonance imaging (MRI).
• The proportion of subjects with no new OCs.
• The rate of new or worsening skeletal deformities.
• The rate of MO-related surgeries.

Additional secondary objectives:
• Overall palovarotene safety.
• The pharmacokinetics of palovarotene at steady state.
• The palatability of drug product when sprinkled onto specific foods.
Exploratory Objectives
Exploratory objectives will be to compare the following effects of palovarotene with placebo:
• The changes in volume of OC cartilage caps as assessed by MRI.
• The rate of new or worsening functional limitations.
• Pain and pain interference due to OCs.
• Quality of life.

Study design

Study PVO-2A-201 will be a multicenter, randomized, double-blind, placebo controlled study assessing various aspects of disease progression in pediatric subjects with MO. The primary efficacy analysis will compare the effect of two palovarotene dosage regimens with placebo on the rate of new OCs over 2 years. The study will also compare the changes from baseline in the total volume of OCs as assessed by MRI, the rate of new or worsening skeletal deformities, the rate of new or worsening functional limitations, the rate of MO-related surgeries, pain due to OCs, and quality of life. To ensure consistency in assessments of OCs and deformities, imaging by whole body MRI and radiographs of the upper and lower extremities will be interpreted by a treatment-blinded central imaging laboratory using standardized procedures.
For sites in the European Union, subjects from 7 to 15 years of age may be enrolled first. Younger subjects (2 to <7 years of age) will be enrolled after the 6-month bone safety data from at least 20 skeletally immature subjects in the palovarotene fibrodysplasia ossificans progressiva (FOP) program are deemed favorable by the independent Data Monitoring Committee (DMC).
Prior to enrollment, tolerance for the MRI procedure will be assessed in subjects <=7 years of age and in subjects who are deemed by the Investigator to require procedural sedation. A pediatric sedation team will perform assessments of the level of procedural sedation the subject may require to complete an MRI session.
At baseline, eligible subjects will be examined with whole body MRI and

radiographs of the upper and lower limbs to determine the number, size, and location of OCs, joint deformities, and other skeletal abnormalities.
On Study Day 1, eligible subjects will be randomized 1:1:1 to one of two active treatments (weight-adjusted daily dose equivalent to 2.5- or 5.0-mg palovarotene, administered orally) or placebo, stratifying by age, sex, and Ext1/2 mutation. Alternating on-site and remote visits (eg, at home or at a local medical facility) will occur every 3 months unless the Investigator deems that a site visit is necessary. Urine pregnancy tests will be performed each month for females of childbearing potential. At the site visits every 6 months, most procedures performed at baseline (including knee and hand/wrist radiographs for the assessment of growth plates and dual x-ray absorptiometry [DXA]) will be repeated. Whole body MRIs and upper/lower limb radiographs will be performed every 12 months. Subjects will undergo all assessments and procedures specified in the Schedule of Assessments provided in Table 1.
At the end of the study, subjects will have the option of participating in an open-label extension study (PVO-2A-202).

Intervention

Palovarotene is supplied as powder-filled hard gelatin capsules. The capsules may be swallowed whole or opened and the contents added onto specific foods as specified in the dosing instructions.

Study burden and risks

The study medicine may cause side effects and discomforts.
The most frequent side effects associated with palovarotene, including those reported so far in studies evaluating palovarotene include effects on skin and mucous membranes (e.g. the inside of your nose and mouth), including: dry skin, dry lips, itching, rash, redness of the skin, flaking, peeling or scratching of skin, inflammation of the lips, dry mouth, dry eyes, hair loss,
Additional side effects include muscle aches, nausea, headaches feeling irritable, anxious and tired, and dizziness.

During the study the following procedures will be done:
Knee and hand/wrist radiograph for assessment of growth plate at screening and at 4 visits, ECG at screenng and at 3 visits, MRI at 3 visits, Radiographs of upper/lower limbs (weight bearing) at 3 visits and DEXA at 5 visits.

Furthermore, subjects will be asked to complete questionnaires. Questions will be raised about how subject is feeling and other medicines taking.
Blood samples, including PK samples will be taken. This may require an overnight stay at a hotel close to the hospital. If applicable pregnancy tests will be performed.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Written, signed, and dated informed subject/parent consent and age appropriate assent (performed according to local regulations)., 2. A clinical diagnosis of MO with a disease-causing Ext1 or Ext2 mutations confirmed by a central laboratory., 3. Male and female subjects with a chronological age of 2-14 years, inclusive., 4. Female subjects must be premenarchal at screening., 5. Bone age at screening of <=14 years, 0 months per the Greulich-Pyle method as assesed by a central reader., 6. Symptomatic MO, defined as the occurrence of any one of the following at screening:, • Five or more clinically-evident OCs and the presence of a new or enlarging OC in the preceding 12 months.
• Five or more clinically-evident OCs and the presence of a painful OC.
• A skeletal deformity.

• A joint limitation.
• Prior surgery for a MO-related complication., 7. If a subject had a prior surgery for MO, the subject should not be screened until at least 8 weeks post-surgery to allow for at least 12 weeks of stabilization of symptoms prior to first dose. Surgical orthopedic implants are allowed if they were in situ for >=12 weeks prior to the baseline MRI., 8. If a subject is currently receiving pain medications, the dose must be stable (ie, <20% variance) for 2 weeks prior to screening., 9. The ability to undergo whole body MRI with or without sedation/general anesthesia., 10. Male and female subjects of child bearing potential who are heterosexually active must agree to use two highly effective methods of birth control, one of which must be highly effective during treatment, and for 1 month after treatment discontinuation, unless they commit to true abstinence from heterosexual sex. Heterosexually active females of child bearing potential (FOCBP) must also agree to start effective methods of birth control at screening. An FOCBP is defined as a female who is 13 or older of age or is post-menarchal, whichever is earlier, 11. Subjects must be accessible for treatment with study drug and follow-up.

Exclusion criteria

1. A weight <10 kg., 2. Other known syndromic conditions such as Langer-Giedion or Potocki Shaffer., 3. Any subject with neurologic signs suggestive of spinal cord impingement., 4. If subject is currently using vitamin A or beta carotene, multivitamins containing vitamin A or beta carotene, or herbal preparations, fish oil, and unable or unwilling to discontinue use of these products during palovarotene treatment. For eligibility, no washout is required prior to the first dose of study drug., 5. Exposure to synthetic oral retinoids within 4 weeks prior to enrollment., 6. Concurrent treatment with tetracycline or any tetracycline derivatives, due to the potential increased risk of pseudotumor cerebri., 7. History of allergy or hypersensitivity to retinoids, gelatin or lactose (other than lactose intolerance)., 8. Concomitant medications that are strong inhibitors or inducers of cytochrome P450 (CYP450) 3A4 activity., 9. Amylase or lipase >2 times the above the upper limit of normal (>2×ULN) or with a history of chronic pancreatitis., 10. Elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >;2.5x ULN., 11. Fasting triglycerides >400 mg/dL with or without therapy., 12. Subjects with uncontrolled cardiovascular, renal, hepatic, pulmonary, gastrointestinal, endocrine, metabolic, ophthalmologic, immunologic, psychiatric, or other significant disease. These include subjects requiring glucocorticoid at doses >0.2mg/kg or up to 10 mg prednisone equivalent daily. , 13. Subjects experiencing suicidal ideation (type 4 or 5) or any suicidal behavior within the past month or any suicidal behavior within the past year as defined by the Columbia-Suicide Severity Rating Scale (C SSRS)., 14. Subjects unable or unwilling to complete the study or all study-related procedures, including imaging., 15. Any surgical implant that is contraindicated for MRI. Dental braces are permitted., 16.

Participation in any clinical research study within 4 weeks prior to enrollment or simultaneous participation in any clinical research study., 17. Any reason that, in the opinion of the Investigator, would lead to the inability of the subject and/or family to comply with the protocol.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	22-03-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Palovarotene
Generic name:	Palovarotene

Ethics review

Approved WMO

Date:	05-11-2018
Application type:	First submission

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-11-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-03-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-05-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	04-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-07-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-12-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-01-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-03-2020
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-03-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-002751-28-NL
ClinicalTrials.gov	NCT03173560
CCMO	NL67312.028.18

Study results

Date completed:	02-07-2020
Results posted:	14-09-2021

Summary results
Trial ended prematurely

First publication
29-08-2021